RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 08/01/07, 09/20/07 and 10/29/07 in response to the non-final Office Action mailed 02/01/07.

Status of Claims

2) Claims 126, 128, 129 and 144 have been amended via the amendment filed 08/01/07.

New claims 148-156 have been added via the amendment filed 08/01/07.

Claims 140-143 and 145-147 have been canceled via the amendment filed 08/01/07.

Claims 132-134 have been amended via the amendment filed 10/29/07.

Claims 126 and 144 have been amended via the amendment filed 10/29/07.

Claims 126-131, 144 and 148-156 are pending.

Claims 151-156 have been withdrawn from consideration based upon election by original presentation. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 126-131, 144 and 148-150 are under examination.

Substitute Sequence Listing

3) Acknowledgment is made of Applicants' substitute sequence listing which has been entered on 02/22/08.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraphs 7(a) and 7(b) of the Office Action mailed 02/01/07 is withdrawn in light of Applicants' amendments to the specification.

6) The objection to claim 126 and those claims that depend therefrom and the objection claim 144 made in paragraph 15 of the Office Action mailed 02/01/07, is withdrawn in light of Applicants' amendment to the claims.

Objection(s) Maintained

7) The objection to the specification made in paragraph 7(c) of the Office Action mailed 02/01/07 is maintained for reasons set forth therein.

8) The objection to the specification made in paragraph 7(d) of the Office Action mailed 02/01/07 is maintained for reasons set forth therein and herein below. The amino acid composition of SEQ ID NO: 27 in the substitute sequence listing filed 09/20/07 continues to be inconsistent with the amino acid composition of SEQ ID NO: 27 as depicted in Figure 1D. It is once again suggested that Applicants examine every sequence in the Figures and the specification to make sure that their composition is consistent with those listed in the raw sequence listing.

Rejection(s) Withdrawn

9) The rejection of claims 126, 144 and those dependent therefrom made in paragraph 8 of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the claims and Applicants' arguments.

10) The rejection of claims 126 and 144 made in paragraph 11(a) of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

11) The rejection of claims 126 and 144 made in paragraph 11(b) of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

12) The rejection of claim 128 made in paragraph 11(c) of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claim 129 made in paragraph 11(d) of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

14) The rejection of claim 129 made in paragraph 11(e) of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

15) The rejection of claims 127-131 made in paragraph 11(f) of the Office Action mailed 02/01/07 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

16) The rejection of claims 126, 127, 130, 131 and 144 made in paragraph 13 of the Office Action mailed 02/01/07 under 35 U.S.C. § 102(a) as being anticipated by of Mukamolova *et al*. (*Arch. Microbiol*. 172: 9-14, July 1999) (Mukamolova *et al*., 1999) as evidenced by Mukamolova *et al*. (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al*., 1998), is withdrawn in light of the withdrawal of the new matter rejection.

Objection to Specification

17) 37 CFR 1.75(d)(1) provides, in part, that 'the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.'

The instant specification is objected to for the following reason:

Claim 128, as amended, includes the new limitations: 'bacterial cell is present in a sample, and the method identifies' a microbial infection 'in the sample'. Claim 129, as amended, includes the new limitations: 'cell is present in a patient'. What is now claimed in these amended claims lacks clear support or antecedent basis in the specification.

Rejection(s) Maintained

18) The rejection of claims 126-131 and 144 made in paragraph 9 of the Office Action mailed 02/01/07 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and herein below.

New claims 148-150 are now included in this rejection.

Applicants submit the following arguments:

(A) Applicants point to page 34, line 21 to page 35, line 3 and state that using sequence information relating to *M. luteus* RP-factor, Applicants have identified RP factor proteins from other bacteria, including SEQ ID NO: 2 from *M. tuberculosis*, that share sequence identity with *M. luteus* RP-factor. This information has been used to identify conserved structural features.

(B) Applicants point to Figure 1A and page 34, line 21 to page 35, line 4 of the specification and state that they have identified two RP-factors from *M. luteus* and *M. tuberculosis*.

Additionally, Applicants have identified RP-factors from *M. leprae, Streptomyces coelicolor, Streptomyces rimosus, Mycobacterium smegmatis*, which include four similar genes, and *Mycobacterium bovis* and *Corynebacterium glutamicum,* which include two similar genes.

(C) In Figures 9A and 9B and lines 5-34 of page 35, Applicants have provided an alignment of RP factor proteins in Figure 1A, which identifies conserved structural features and highly conserved amino acid residues. Applicants found that RP-factors share a secretory signal sequence and a conserved 70-residue segment that 'may' act as a signalling domain (lines 5-18 of page 35), which domain includes four conserved tryptophan residues and two conserved cysteine residues that 'may' form a disulfide bridge (lines 25-30 of page 35). These structural features are conserved among a wide variety of proteins and are therefore 'likely to be functionally important'. Accordingly, Applicants' specification provides guidance relating to those regions of the protein where sequence variations are 'likely to be tolerated' and those conserved regions where variations in the sequence are less desirable.

(D) One of skill in the art could readily identify those variant polypeptides that fall within the scope of Applicants' claims, i.e., those polypeptides having at least 20%, 50%, 85%, 90%, or 95% amino acid sequence identity to SEQ ID NO: 2 that are capable of resuscitating dormant bacteria using routine methods that are clearly described in Applicants' specification.

(E) Applicants' specification at page 33, line 20 to page 34, line 3 and page 35, lines 35-44 clearly describes methods of screening for polypeptides capable of resuscitating dormant bacteria using purified RP-factors. Such screening does not constitute undue experimentation MPEP 2164.06 and *In re Wands*, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Thus, using no more than routine methods, the skilled artisan could readily identify those polypeptides having at least 20% identity to SEQ ID NO: 2 that are capable of resuscitating dormant bacteria.

(F) Applicants point to page 35, lines 35-44 and state that they have plainly disclosed a biological activity for SEQ ID NO: 2 including that portion of the polypeptide containing amino acids 117-184. Applicants describe the stimulation of growth of *M. luteus* and *M. tuberculosis* cell cultures *in vitro* by purified SEQ ID NO: 2.

(G) Applicants state that they submit: (i) additional data in Exhibit A showing that

polypeptides having about 20% identity to *M. luteus* RP-factor have a biological activity associated with *M. luteus* RP-factor; and (ii) recent work show that Rp-factor proteins are murein hydrolases having cell wall lytic activity which is 'likely' to be important for resuscitating dormant, moribund or latent bacterial cells which contain an excess of an inert peptidoglycan. Applicants opine that: (a) The cell wall lytic enzyme activity is required to make a restricted number of scissions in the cell wall, thereby allowing bacterial cell growth and wall expansion to occur; (b) Bacteria 'may' become dormant due to a reduction of nascent peptidoglycan in the bacterial cell wall and its gradual replacement by inert peptidoglycan; and (c) Cleavage of the cell wall 'likely' provides for resumption of cell wall synthesis and the subsequent re-initiation of protein synthesis, which is important for the resuscitation of dormant, moribund or latent bacterial cells.

(H) Applicants state that: (i) Figures 1 and 2 from Exhibit A provide sequence alignments of proteins having about 20% identity to RP-factor; (ii) Figure 2 shows a sequence alignment of the Rpf-like domain of a *T. whipplei* enzyme, TW325, with other Rpf domain sequences, the percent homology of which ranges between 20% to 28.8%; (iii) Figure 3 is a gel zymogram showing that TW325 has murein hydrolytic activity; (iv) A suspension of *M. luteus* cell wall fragments loses up to 50% optical density following incubation with recombinant Rpf and provides evidence that Rpf has cell wall lytic activity; (v) Diaminopimelic acid-containing material is released into the soluble fraction using fluorescent-labeled cell walls; (vi) and Figure 4 shows that both Rpf proteins and TW325 have murein hydrolytic/cell wall activity.

(I) Table 2 and Experiment III show that a *M. luteus* Rp-factor was able to stimulate the growth of *M. tuberculosis* cells that failed to show viability. Applicants argue that in view of this disclosure, Applicants have clearly enabled methods of resuscitating bacterial cells in a sample or a patient.

Applicants' arguments have been carefully considered, but are not persuasive. Applicants repeatedly identify lines 35-44 of page 35 of the specification as providing the enabling disclosure. However, page 35 of the instant specification does **not** contain lines beyond line 31. The specification at page 33, line 20 to page 34, line 3 describes RP-factor antibodies and RP-factor antagonists or inhibitors, and therefore has nothing to do with the instantly claimed method. What are claimed in the instant claims are not RP-factors from *M. luteus, M. tuberculosis, M. leprae,*

Streptomyces coelicolor, Streptomyces rimosus, or *Mycobacterium smegmatis*, or their similar genes, or a biologically active SEQ ID NO: 2 from *M. tuberculosis* that shares sequence identity with *M. luteus* RP-factor, instead, a method for resuscitating dormant, moribund or latent bacterial cells comprising contacting the bacterial cells with an isolated polypeptide at least 50%, 90% or 95% identical to amino acid residues 117-184 of SEQ ID NO: 2. The resuscitation of dormant, moribund or latent bacterial cells in the claimed method is not limited to *in vitro* resuscitation, but encompasses *in vivo* resuscitation in a generically recited 'patient'. The resuscitation of bacterial cells present in a 'patient' by the claimed method includes *in vivo* contacting in a patient or *in vivo* administration of the recited polypeptide variant to a patient. See claim 129. The broad limitation 'a sample' in the dependent claim 128 includes biological and non-biological samples, environmental samples etc. Similarly, the broad limitation 'patient' in the dependent claim 129 encompasses a human and non-human patient having any of a plethora of microbial or non-microbial infections, cancer, autoimmune diseases, or medical/clinical conditions of any and all kinds. However, there is absolutely no evidence within the instant specification enabling such a method. It should be noted that the polypeptide used in the method claims that are currently under examination is required to be isolated, but not purified. The disclosure in the specification is limited to the *in vitro* addition of a purified RP-factor protein from *M. luteus* or Rpf2 from *M. tuberculosis* to *in vitro* cultures of *M. luteus* or *M. tuberculosis,* wherein the purified protein stimulated the *in vitro* growth of cultured cells of said bacteria. See Figure 10 and also Figure 6.

It is well recognized among those of skill in the art that assigning functional activities for any particular protein or a family of proteins based upon sequence homology is inaccurate, partly because of the multifunctional nature of proteins. See abstract; and page 34 of Skolnick *et al.* (*Trends in Biotechnology* 18: 34-39, 2000, already of record). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein. See abstract and Box 2 of Skolnick *et al.* In the instant application, the recited genus of polypeptide variants having at least 50%, 90% or 95% identity with amino acid residues 117 to 184 of SEQ ID NO: 2 have been assigned the functional capacity of resuscitating dormant, moribund, or latent bacteria of any genus or species. However, there is no showing of a definitive nexus between murein hydrolase activity or the alleged cell wall lytic activity of the recited genus of polypeptide

variants having at least 50%, 90% or 95% identity with amino acids 117 to 184 of SEQ ID NO: 2 and its relationship to resuscitation of dormant, moribund or latent bacterial cells, including highly virulent, pathogenic, and/or drug-resistant bacterial cells *in vivo* in a patient, or *in vitro* in a sample to identify a microbial infection in the sample. Applicants only speculate that the cell wall lytic activity is 'likely' to be important for resuscitating dormant, moribund or latent bacterial cells. See paragraph bridging pages 13 and 14 of Applicants' amendment filed 08/01/07. The alleged presence of excess of an inert peptidoglycan in the walls of dormant bacterial cells, its alleged restraints on the growth of the bacteria, the alleged requirement for the cell wall lytic enzyme activity to make 'a restricted number' of scissions in the cell wall thereby allowing cell growth and wall expansion as stated in the paragraph bridging pages 13 and 14 of Applicants' amendment filed 08/01/07 do not provide the disclosure and/or guidance enabling the instantly claimed method. There is no showing that the recited genus of polypeptide variants having at least 50%, 90% or 95% identity with amino acids 117 to 184 of SEQ ID NO: 2 have the capacity to make 'a restricted number' of scissions in the cell wall of dormant, moribund or latent bacterial cells of any generic bacterial cells *in vivo* in a patient or *in vitro* in a sample and the resultant 'restricted number' of scissions in the bacterial cell walls results in resuscitation of said dormant, moribund or latent bacterial cells. The specific regions or amino acid residues within the amino acids spanning 117 to 184 of SEQ ID NO: 2 that are associated with the alleged capacity to make 'a restricted number' of scissions in the cell wall of dormant, moribund or latent bacterial cells of any generic bacterial cells *in vivo* in a patient or *in vitro* are not identified, without which one of skill in the art would not be able to avoid alterations or substitutions in those regions, or among amino acid residues within positions 117 to 184 of SEQ ID NO: 2 while producing species of the genus of polypeptide variants having at least 50%, 90% or 95% identity with amino acids 117 to 184 of SEQ ID NO: 2 to practice the claimed method. Furthermore, the identification of any microbial infection in a biological or non-biological sample or in a patient upon contacting dormant, moribund, or latent bacterial cells of the vast genus of bacteria and thereby resuscitating said dormant, moribund, or latent bacterial cells in said sample or said patient is simply not enabled within the instant specification. The precise structure of the isolated polypeptide having at least 50% identity to amino acid 117-184 of SEQ ID NO: 2 and the precise amount of said polypeptide that is needed for making a restricted number of scissions in the cell wall that would result

particularly in the *in vivo* resuscitation of said dormant, moribund, or latent bacterial cells, is not disclosed. The alignment of the domain structures of the various proteins as depicted in Figures 9A and 9B; or the post-filing sequence identity/homology and the zymogram result submitted via Exhibit A, are insufficient to establish a clear nexus between murein hydrolase activity of the recited genus of polypeptide variants having at least 50%, 90% or 95% identity with amino acids 117 to 184 of SEQ ID NO: 2 and its direct role or connection with resuscitation of dormant, moribund or latent bacterial cells, including highly virulent, pathogenic, and/or drug-resistant bacterial cells *in vivo* in a patient, or *in vitro* in a sample to identify a microbial infection in the sample. Even if one produced a series of polypeptide variants having at least 50% sequence identity with amino acids 117 to 184 of SEQ ID NO: 2 and used them to contact dormant, moribund or latent, taxonomically and genetically divergent pathogenic or non-pathogenic bacterial cells *in vitro* or *in vivo*, there is no predictability that these polypeptide variants would retain the capacity to make a restricted number of scissions in the cell wall of said bacterial cells, particularly *in vivo,* and resuscitate said dormant, moribund, or latent bacterial cells. This is important because predictability or unpredictability is one of the *Wands* factors for enablement. The specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. As set forth previously, the state of the art at the time of the invention was also limited to certain unsubstantiated or unproven speculations with regard to the potential use of Rpf-like proteins in detection (or diagnosis), treatment, and prophylaxis. For instance, Mukamolova *et al*. (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al*., 1998) stated that it was 'tempting to speculate' that resuscitation and growth of the very significant re-emerging pathogen *Mycobacterium tuberculosis* and possibly of *Mycobacterium leprae* 'may be' controlled in part at least by members of a family of secreted Rpf-like proteins that function as autocrine and/or paracrine growth factors. See last paragraph in left column on page 8921 of Mukamolova *et al*. (1998). In July 1998, Mukamolova *et al*. concluded as follows:

> Further experimental work will be required to explore these hypotheses, which may lead, in the short term, to substantially improved laboratory methods for the detection and cultivation of these organisms and in the longer term, to therapeutic strategies and vaccines for preventing their growth *in vivo*.

Thus, neither the instant specification, nor the art at the time of the invention is enabling of the instantly claimed method. Therefore, undue experimentation would have been required by one of skill in the art at the time of the effective filing date of the instant application to reproducibly

practice the invention as claimed due to the lack of specific and adequate disclosure, the lack of working examples enabling the full scope, the art-demonstrated unpredictability, the quantity of experimentation necessary, and the breadth of claims. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C. § 112, first paragraph. The rejection stands.

Rejection(s) under 35 U.S.C. § 102 Maintained

19) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20) The rejection of claims 126, 127, 130, 131 and 144 made in paragraph 14 of the Office Action mailed 02/01/07 under 35 U.S.C. § 102(b) as being anticipated by of Mukamolova *et al*. (*Antonie van Leeuwenhoek* 67: 289-295, 1995) (Mukamolova *et al*., 1995) as evidenced by Mukamolova *et al*. (*PNAS* 95: 8916-8921, July 1998 – Applicants' IDS) (Mukamolova *et al*., 1998), is maintained for the reasons set forth therein and herein below.

New claims 148 and 149 are now added to this rejection.

Applicants cite case law and contend that to serve as an anticipation, a cited reference must describe all of the elements of the claimed invention. Applicants state that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or *inherently described*, in a single prior art reference. Applicants acknowledge that Mukamolova *et al*. (1995) describe the use of a culture supernatant from *Micrococcus luteus* bacterial cells to resuscitate dormant bacterial cells. Applicants argue that their claims are directed to the use of an isolated polypeptide having at least 20%, 50%, 85%, 90%, or 95% identity to SEQ ID NO: 2, an RF-factor polypeptide of *M. tuberculosis*, to resuscitate dormant bacterial cells. Applicants submit that Mukamolova *et al*. (1995) fail to describe the use of any isolated polypeptide or the use of any *M. tuberculosis* polypeptide and therefore fail to anticipate the claimed invention.

Applicants' arguments have been carefully considered, but are not persuasive. As recited currently, the isolated polypeptide comprising at least 50%, 90%, or 95% identity to SEQ ID NO: 2 is not required to be a polypeptide from *M. tuberculosis*, but encompasses such a polypeptide of

any microbial origin or even of synthetic origin. What is required for anticipation is the structural identity between the prior art polypeptide and the instantly recited polypeptide irrespective of its source. The limitation 'polypeptide comprising at least …% identity' is not required to be a polypeptide having at least …% 'sequence' or structural identity. As set forth previously, Mukamolova *et al*. (1995) taught a method of resuscitation of starved or dormant cells in *Micrococcus luteus* stationary cultures by contacting the dormant cells with a sterile-filtered supernatant isolated from the late log phase of viable cultures of the same *Micrococcus luteus* which supernatant contains an antibacterial factor secreted or expressed by the *Micrococcus luteus* cells, or by contacting with the resuscitating cells of *Micrococcus luteus* secreting or expressing an antibacterial factor. The antibacterial factor secreted or expressed by the *Micrococcus luteus* cells is separated from the cells and therefore is isolated. The sterile supernatant containing the non-cellular or isolated antibacterial factor is contained in a minimal medium, i.e., a pharmaceutically acceptable carrier suitable for local or systemic administration. The strain of viable and dormant *Micrococcus luteus* used by Mukamolova *et al*. (1995) is the 'Fleming strain 2665' or NCIMB 13267 strain. See title; abstract; Materials and methods; Results; and Figure 2. The prior art 'Fleming strain 2665' of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants (see last paragraph on page 44 of the instant application), and therefore, the prior art strain is expected to necessarily to comprise a nucleic acid that encodes the recited polypeptide. Because the 'Fleming strain 2665' strain of *Micrococcus luteus* is the very same strain used in the instant invention by Applicants, the cells of this strain is expected to necessarily secrete or express the instantly recited polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2, and the supernatant isolated from its culture is expected to necessarily contain the secreted polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2. That the prior art culture supernatant necessarily comprises the instantly recited polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2 in a unit dosage form is inherent from the teachings of Mukamolova *et al*. (1995) in light of what is known in the art. For instance, Mukamolova *et al*. (1998) teach that the culture supernatant of viable cells of the 'Fleming strain 2665' of *Micrococcus luteus* contains or secretes a proteinaceous resuscitation promoting factor that comprises the instantly recited polypeptide having at least 50% identity to amino acid residues 117 to 184 of SEQ ID NO: 2 and promotes the

resuscitation and growth of dormant cells of the homologous organism in picogram quantities. See abstract; Materials and Methods; Results; and Figures 2 and 3 of Mukamolova *et al*. (1998). Thus, Mukamolova *et al*. (1995) taught all of the elements of the claimed invention and therefore anticipate the instantly claimed method.

Furthermore, it should be noted that extra references and extra evidence can be used to show that the primary reference contains an enabling disclosure and that a characteristic not disclosed in the reference is inherent therein. See MPEP 2131.01. 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co*., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc*., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). Also note that the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP 2124. In the instant application, Applicants have not advanced any arguments with regard to the extra evidence provided via the teachings of Mukamolova *et al*. (1998). The rejection stands.

Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

21) Claims 128 and 129 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 128, as amended, includes the new limitations: 'bacterial cell is present in a sample, and the method identifies' a microbial infection 'in the sample'. Applicants state that support for the amendment to claim 128 is found at page 21, lines 27-44 of the specification. However, page 21 does not contain lines 32-44. Lines 27-31 of page 21 reproduced below are not supportive of

the now added claim limitations, and do not recite a bacterial cell present in a sample, and the claimed method identifying a microbial infection in the sample:

> receptors/convertases of the invention.
>
> The term "homologue" is used herein in two distinct senses. It is used *sensu stricto* to define the corresponding protein from a different organism (i.e. a species variant), in which case there is a direct evolutionary relationship between the protein and its

Claim 129, as amended, includes the new limitations: 'cell is present in a patient'. Applicants state that support for the amendment to claim 129 is found at page 23, lines 35-40. However, page 23 does not contain lines 35-40. Therefore, the identified limitation(s) in the claim(s) and the currently claimed scope of the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific pages and lines of the disclosure, as originally filed, for the limitation identified above, or alternatively, remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

22) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

23) Claims 128, 129, 148 and 149 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 128, as amended, is indefinite because it has improper antecedent basis in the limitation: 'said bacterial cell'. Claim 128 depends from claim 126, which recites 'bacterial cells', but not any bacterial cell. For proper antecedent basis, it is suggested that Applicants replace the above-identified limitation with the limitation --said bacterial cells--.

(b) Analogous rejection and criticism apply to claim 129.

(c) Claim 128, as amended, is further indefinite and confusing in the limitation: 'the method identifies a microbial infection in the sample', because it in unclear how 'a sample' can be 'infected'. Does it mean that the recited sample is contaminated by a microbe? Clarification is requested.

(d) New claims 148 and 149 are vague and indefinite in the limitation: 'polypeptide comprises at least …% identity', because it is unclear what identity is encompassed in this limitation. Does '…% identity' include % sequence identity, % functional identity, % immunospecific identity, % conformational identity, or % physicochemical identity?

Remarks

24) Claims 126-131, 144 and 148-150 stand rejected.

For clarity, it is suggested that Applicants delete the limitation 'comprising a sequence' from line 3 of claim 144.

25) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

26) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted to the Office' Central Rightfax number 571-273-8300 via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week.

27) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

28) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Acting supervisor, Shanon Foley, can be reached on (571) 272-0898.

/S. Devi/
S. Devi, Ph.D.
Primary Examiner
AU 1645